36 discuss the types of disease conditions in which the **Cummins** patent might be employed, namely: "...apparent autoimmune disorders characterized by a chronic tissue degenerative inflammatory condition. Diseases so characterized include multiple sclerosis, rheumatoid arthritis, stomatitis, and lupus erythematosus." Conditions supported by actual clinical data in the prior art are predominantly veterinary applications, such as "canine lupus erythematosus".

Of the human cases pertaining to autoimmune conditions, there is only one anecdotal report of a multiple sclerosis patient that had been treated. The remainder are cases that are either clearly not autoimmune conditions (cancers, acne, viral warts) or maladies for which an autoimmune etiology remains controversial (rheumatoid arthritis, stomatitis).

Applicant argues this limited clinical data is far from enabling and hence cannot be considered anticipatory. **Cummins** describes in column 12 that a female with multiple sclerosis "received treatment in accordance with the present invention" and "had no recurrence...for the past nine months". Apart from the consideration that such a disorder is characterized by remission and

relapse, as is known in the art, **Cummins** provides absolutely no credible evidence of efficacy or that such an invention could be made or was in fact made. Similarly, the **Cummins** descriptions of treating malignant lymphoma, mesothelioma and apthous stomatitis are also anecdotal. A person having ordinary skill in this art would clearly consider these anecdotal descriptions as literally incredible and therefore non-enabling.

As the Supreme Court held in *Seymour v. Osbourne*, 78 U.S. (11 Wall.) 516 (1870) a non-enabling reference is not anticipatory prior art under 35 USC § 102. See, also, *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 1 USPQ2d 1241 (Fed. Cir. 1986); *In re Wiggins*, 179 USPQ 421 (CCPA 1973); *In re Brown* 141 USPQ 245 (CCPA 1964). That is, to be an anticipatory reference under 35 USC §102, the prior art must be enabling to the same degree as an invention seeking patent protection under 35 U.S.C §112, first paragraph.

The instant invention targets a much broader spectrum of autoimmune conditions than **Cummins**, and, more importantly, presents substantive clinical data in support. In marked contrast to the one multiple sclerosis patient presented in the prior art, the

instant invention contains data from 27 multiple sclerosis patients and 18 control patients. Animal data presented is that for two well-established models of human autoimmune disease, experimental allergic encephalitis/neuritis and the NOD mouse, a model for human autoimmune diabetes mellitus.

Further, the **Cummins** claims (cited by Examiner in support of the 35 USC §102 rejection) are completely limited to treating viral diseases. Applicant respectfully submits that the instant invention as presently claimed falls outside the scope of the **Cummins** disclosure. **Cummins** repeatedly emphasizes the criticality of maintaining the interferon in contact with the oral and pharyngeal mucosa for the purposes of treating viral diseases. Applicant's claims specifically point out that the method requires ingestion of the interferon. Indeed, Applicant's specification shows the necessity of the interferon interacting with intestinal sites and Peyer's patches.

The first section of **Cummins** cited by the Examiner (col. 4, lines 19-36) in support of the under 35 U.S.C. §102(b) presents the suggested dosage for the therapeutic agent of the **Cummins** patent. This is much different than the one presented in

the instant invention—"...more preferably 0.5 to about 1.5 IU/lb of body weight per day" as compared to 50–25,000 IU/kg every other day.

Finally, with respect to the route of administration presented in col. 4, lines 19-36, Claim 1 of the instant invention states: "A method of treating an auto-immune disease in an animal comprising the step of orally administering a type one interferon to said animal **such that the type one interferon is ingested after oral administration.**" (emphasis added). This is clearly distinct from the prior art, which emphasizes a different mode of absorption:

> "...in a dosage form adapted to promote contact of said dosage of interferon with the oral and pharyngeal mucosa of said animal." (emphasis added).

As one of the accompanying 37 CFR Rule 1.132 Declarations points out, **Cummins** "stresses that administration of interferon should be directed at absorption through the oral mucosa, and not the gastric mucosa. Maximal contact with the oral or pharyngeal mucosa is emphasized, contact with the gastric or intestinal mucosa is considered therapeutically nugatory." This is

contrasted with Applicants' invention, in the other accompanying 37 CFR Rule 1.132 Declaration: "In Applicant's animal experiments, **the interferon was fed through a needle inserted directly into the stomach or duodenum of the animal, i.e., there was no contact with the oral or pharyngeal mucosa.** In Applicant's clinical studies with human subjects, the interferon was "ingested", which briefly exposed the oral mucosa to the interferon, but **no attempts at maximizing contact with the oral mucosa were made nor would there have been any significant absorption of the alpha-interferon through the oral or pharyngeal mucosa**." (emphasis added).

Examiner also cites to col. 5, lines 50-55 of the **Cummins** patent in support of the rejection of Claims 1-5 and 6-7 under 35 U.S.C. §102(b). This section teaches the dosage of the therapeutic agent, viz.:

> "Daily dosage of interferon can be administered as a single dosage, or, preferably, it is divided and administered in a multiple-dose daily regimen. A staggered regimen, for example one to three days treatment per week or month, can

be used as an alternative to continuous daily treatment." (emphasis added).

Applicant contends that this does not anticipate the instant invention, as it teaches a multiple-dose daily regimen. Additionally, the descriptive clinical lore of the **Cummins** patent can in no way be said to anticipate the substantive data presented in the instant invention.

Examiner further cites **Cummins** at col. 6, lines 12-26 to support the rejection of claims 1-5 and 6-7 under 35 U.S.C. §102(b). Applicant argues that this is an explicit teaching away from the present invention. Lines 12-16 of col. 6 make this point clearly:

> "It is also contemplated by the present invention to provide interferon in a solid dosage form such as a lozenges (sic) adapted to be dissolved upon contact with saliva in the mouth with or without the assistance of chewing."

As stated in Applicant's specification, the interferon dosage can by-pass the mouth, see, e.g. Example 11. As stated *supra*, interferon is orally administered by placing a 2.5 cm syringe fitted with a 20 gauge ball point needle in the posterior oropharyngeal region of the oral cavity and delivering the type one

interferon dose directly to the distal esophagus, stomach, and proximal small intestine (as verified experimentally by injecting Evans blue during routine feeding and subsequent sacrifice). Thus, Applicant maintains that there are substantive differences between the method of **Cummins** and the Applicant's claims that the **Cummins** patent. Declarations under 37 CFR 1.132 are provided herewith, which support and extend Applicant's arguments. Accordingly, Applicant respectfully requests that the rejection of Claims 1-5 and 6-7 under 35 U.S.C. §102 as being anticipated by **Cummins** be withdrawn.

The 35 U.S.C. §103 Rejections:

Claim 5 stands rejected under 35 U.S.C. §103 as being unpatentable over **Cummins, Jr.** (US Patent 5,019,382). This rejection is vigorously traversed.

As stated above, **Cummins** teaches the dosage of the therapeutic agent:

> "Daily dosage of interferon can be administered as a single dosage, or, preferably, it is divided and administered in a multiple-dose daily regimen. A staggered regimen, for

example one to three days treatment per week or month, can be used as an alternative to continuous daily treatment." (emphasis added).

Applicant contends that the dosage regimen delineated in Claim 5 is not rendered obvious by **Cummins** The instant invention teaches an every other day dosing. This is alluded to as a less preferred method of administering interferon by **Cummins,** which teaches a multiple-dose daily regimen.

Examiner further states that claims 1-20 (sic) stand rejected under 35 U.S.C. §103 as being unpatentable over **Cummins** in view of **Shibutani** et al. and the abstracts of **Gross** et al., **Giron** et al. and **WO 94/20122** This rejection is respectfully traversed.

Applicant respectfully asserts that the cited references do not render the present invention obvious under 35 U.S.C. Section §103 for the reasons cited above in response to the 35 U.S.C. Section § 102 rejection. The **Shibutani** abstract is simply a description of a lack of toxicity of human beta interferon in mice and rats. It does not disclose, teach or suggest in any form a method of treating auto-immune disease in an animal comprising the step of orally

administering a type one interferon to said animal such that the type one interferon is ingested after oral administration as disclosed in the instant application.

This issue of dosage is addressed in some detail in both Rule 1.132 Declarations, the most salient aspects of the arguments are recapitulated here. First, one feature of the instant invention is its precise delineation of a dose-response relationship for the oral administration of type I interferons to treat autoimmune diseases. Secondly, there is absolutely no overlap between the doses suggested by **Cummins** and doses found to be effective in the present invention. The latter are significantly higher (by about two orders of magnitude) than the maximum dose of **Cummins**.

The abstract of **Gross** et al. has no relevance to the instant invention. This reference reports the use of alpha interferon, injected subcutaneously, to treat condylomata in a diabetic individual. There is no relationship between the diabetes and the administration of alpha interferon: it is not used to treat the diabetes, nor is any therapeutic effect on the diabetes reported.

The abstract of **Giron** et al. is similarly inapposite. This reference discusses an antiviral effect of interferons in murine

encephalomyocarditis. Diabetes is associated with this viral condition. Neither the route of administration nor the types of interferons are specified.

WO 94/20122 is an abstract for a patent application. It describes methods of treating "an asymptomatic preclinical autoimmune state in a mammal" or inhibiting "rejection of transplanted islet cells or a pancreas in a mammal". These do not pertain to the instant invention.

While **Cummins** describes unsubstantiated anecdotal stories, **Cummins** does not enable Applicant's invention and place Applicant's invention in the hands of a person having ordinary skill in this art. Nor do the other references alone, or in combination with **Cummins**. As both Rule 1.132 Declarations point out, a person with ordinary skill in the art would not have expected interferons to have any clinical effects. Proteins such as interferons are broken down in the gastrointestinal tract when ingested and would be expected to be biologically inactive.

Hence, no such teaching, suggestion or incentive may be gleaned from any of the references relied upon by the Examiner. Thus, Applicant respectfully submits that the cited references do not

render the claimed invention obvious. Accordingly, Applicant respectfully requests that the rejection of Claims 1-20 under 35 U.S.C. §103 be withdrawn.

The 35 U.S.C. §101 Rejections:

Claims 1-7 are provisionally rejected under 35 USC §101 as claiming the same invention as that of copending application Serial No. 08/631470. Claims 8-18 are provisionally rejected as being unpatentable over Claims 1-8 of copending application Serial No. 08/631470 in view of the abstracts of **WO 94/20122**, **Gross** et al. and **Giron** et al.

Should either application be allowed, Applicant will submit a terminal disclaimer in a timely fashion. In the meantime, Applicant respectfully requests that the double-patenting rejections be held in abeyance.

The 35 U.S.C. §112 Rejections:

Claims 8-18 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

Applicant submits that the instant specification adequately describes, defines and supports Applicant's claims 8-18. Claims 8, 12, 16 and 17 have been amended as helpfully suggested by the Examiner. Regarding claim 8, Applicant maintains that the specification specifically delineates both the step of oral administration (see, page 32, lines 22-25, and page 33, lines 1-6) and what defines an 'at-risk population'. Applicant respectfully directs Examiner's attention to page 75 of the Specification, lines 4-8:

> "at-risk populations (non-diabetic relatives of IDDM patients with anti-64kDa autoantibodies including the 65kD isoform, high titers of islet cell antibodies (ICA), and insulin autoantibodies (IAA), in multiplex families)."

With respect to claim, 9, this claim is supported by pages 20 and 40 of the Specification. Claim 10 is supported in the Specification on pages 14 and 20; claim 11, pages 70-74 present empirical data in support of the dosing regimen. Regarding Claim 12, Applicant again avers that the method of oral administration of a type one interferon is adequately described in the Specification. More empirical evidence in support of this claim is found on pages

70-73. Claim 13 is, like Claim 9, fully supported by pages 20 and 40 in the Specification. With respect to Claim 14, pages 14 and 20 of the specification furnish adequate descriptions. Claim 15 recites "The method of Claim 12, wherein said animal is a human." Applicant respectfully argues that this claim is not indefinite. Regarding Claim 16, Applicant reiterates the arguments made for Claim 8 and 12, namely, that both the steps of oral administration and the at-risk population are well defined in the Specification. Further, that which is not specifically described would be readily recognizable to a person having ordinary skill in this art. With respect to Claim 17, pages 20 and 40 again provide adequate description. Finally, regarding Claim 18, the dosage regimen is well supported by the information found on pages 14 and 20 of the Specification. Accordingly, in view of the claim amendments and Applicant's remarks, Applicant respectfully requests that the rejection of Claims 8-18 under 35 U.S.C. §112, second paragraph, be withdrawn.

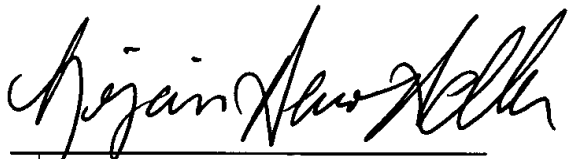
The Specification and Claims have been modified per Examiner's helpful suggestion to consistently employ one abbreviation for the word 'interferon'. Examiner further states that

the term "at-risk population" is inadequately defined in the Specification, and states "...Note that the specification does not give any description of this patient." (Office Action Summary, page 6). Applicant has discussed this point *supra*. Per Examiner's request, a new declaration is also enclosed.

This is intended to be a complete response to the Office Action mailed February 17, 1998. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: 8/17/98



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